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|---|
| LUKTON, DAVID |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/486,062 | Applicant(s) HOLZEMANN ET AL. | |
|---|---|---|---|
| | Examiner David Lukton | Art Unit 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)[X] Responsive to communication(s) filed on *09 May 2002* .

2a)[ ] This action is **FINAL**. 2b)[X] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)[X] Claim(s) *1,2,4-8 and 11-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[X] Claim(s) *1,2,4-8 and 11-34* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1 [ ] Certified copies of the priority documents have been received.

2 [ ] Certified copies of the priority documents have been received in Application No. _____ .

3 [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) [ ] The translation of the foreign language provisional application has been received.

15)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) [ ] Interview Summary (PTO-413) Paper No(s). _____ .
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other: .

Pursuant to the directives of paper No. 18 (filed 5/9/02), claims 1, 2, 4-8, 20, 22-25 have been amended, and claims 32-34 added. Claims 1, 2, 4-8, 11-34 are pending.

Applicants' arguments filed 5/9/02 have been considered and found persuasive in part. The rejection of claims 4 and 24-25 are rejected under 35 U.S.C. 112, first paragraph (lack of possession) is withdrawn.

Upon reconsideration, the prosecution is re-opened; this Office action is non-final.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-8 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In the response filed 5/9/02, it is argued that if a compound is enabled, it follows therefrom that a "composition" which comprises that compound in combination with a pharmaceutically acceptable carrier is enabled as well. Claims 5, 6 and 21 are not directed simply at compositions. Rather, they are drawn to "pharmaceutical compositions". The

term "pharmaceutical" pertains to the formulation and dispensation of drugs, i.e., compounds which have been shown to be therapeutically effective to treat a disease or pathological condition. The response filed 5/9/02 stated that composition claims should not be treated as if they were method claims. Where "pharmaceutical compositions" are concerned, however, it is appropriate to consider what is intended by the term "pharmaceutical", in particular, the effective amount of the active agent and the result that the active agent elicits. One can and should look to the specification to see what therapeutic methods have been asserted. Neither *Union Oil vs Atlantic Richfield* nor *In re Spada* (cited by applicants) discusses the issue of the circumstances under which "pharmaceutical compositions" are enabled, or the circumstances under which "pharmaceutical compositions" are not enabled. By way of contrast, suppose that a researcher has obtained an *in vitro* result on a given compound, and he has a theory about how the physiology of a rat might be altered if that compound were administered to the rat. If the compound is combined with a "pharmaceutically acceptable carrier", the resulting composition is not properly termed a "pharmaceutical composition", since its efficacy in the treatment of a given disease has not yet been determined. Similarly, a result has been obtained *in vitro* using a few of the claimed compounds. The specification offers speculation as to what might happen if one of the claimed compounds were administered to an ill patient. It is asserted that the claimed pharmaceutical compositions will be effective to treat the various disorders that are

recited in claims 7-8, and on page 3, line 31+. These include angiogenic disorders, "thrombosis", myocardial infarct, coronary heart disease, arteriosclerosis, tumors, osteoporosis, inflammation, and "infections". But efficacy in the treatment of these diseases is not established by combining the claimed compounds with a pharmaceutically acceptable carrier. Accordingly, characterizing the compositions as "pharmaceutical compositions" is not appropriate.

In the response filed 5/9/02, it is argued that *Cross v Iizuka* (224 USPQ 740) supports the proposition that "outcomes of treatment" can be predicted based upon *in vitro* data; however, this is not persuasive in all cases. The key issue in *Cross v Iizuka* pertained to a determination of the proper priority date for each application. While claim 8 of USP 4,602,016 is drawn to a "pharmaceutical composition", and claim 40 of USP 4,632,934 is drawn to therapeutic methods, as stated on page 741 of the opinion, the sole "phantom" count of the interference was drawn to compounds *per se*. Thus, the issue before the Court was not whether a claim drawn to a method of treating a disease in an animal (or human) is enabled; the Court assessed issues pertaining to claim that was drawn to a compound *per se*. This does not address the issue of whether a therapeutic method claim would be enabled. Neither party presented evidence that extrapolation from thromboxane synthetase inhibition *in vitro* to treatment of a human disease (e.g., thrombosis, ischaemic heart disease, stroke, migraine, or vascular complications of diabetes) is "unpredictable". Thus,

*Cross v Iizuka* does not support the proposition that where an applicant provides *in vitro* data, and concommitantly asserts therapeutic efficacy based on that *in vitro* data, therapeutic method claims are thereby enabled. *In re Brana* has also been cited. The application at issue matured into U.S. Patent 5,552,544. The claims in that patent are drawn solely to compounds *per se*. There are no method-of-use claims, and no claims drawn to a "pharmaceutical composition". The fact pattern in *Brana* is not commensurate with that of the rejected claims in the instant application.

In citing *Gould v Quigg* (3 USPQ2d 1302, 1987), it is implied that evidence of past failures may not be used in an enablement rejection. *Gould v Quigg* pertained to application 05/823611, which matured into USP 4,704,583. The invention was that of a light amplification apparatus, and the issue was whether the description was enabling. It is not evident from the decision that either party had presented evidence of past failures, or that the Court had issued an opinion regarding the relevance of past failures. The Court did state, however, that "the mere fact that something has not previosuly been done clearly is not in itself a sufficient basis for rejecting all applications purporting to disclose how to do it". This is quite different, however, from an actual showing of unpredictability. Moreover, the issue revolved around a question of chemical engineering, i.e., whether or not a given apparatus could be designed. In the instant case, the compounds have been tested *in vitro*; the question in the instant case is whether such *in vitro* activity is predictive of

therapeutic efficacy. Thus, in *Gould v Quigg*, (a) the issue was one of engineering, rather than therapeutic efficacy, (b) the Court did not say that evidence of unpredictability could not be used as a factor in determining whether a claimed invention is enabled, and (c) no evidence of unpredictability was presented by the Commissioner. Accordingly, *Gould v Quigg* does not negate any of the arguments set forth by the examiner in the instant case.

In citing *In re Bundy* (209 USPQ 48, 1981), it is argued that a claim is enabled if the specification discloses some activity, coupled with knowledge in the art as to the use of this activity. The case at issue is now USP 4461917, which is a divisional of USP 4,060,534. The sole claim at issue is drawn to compounds *per se*, not to a therapeutic use. The compounds of the claim of '917 constitute a small subgenus of the genus of compounds disclosed in '534, most of which were found to be novel and enabled. The question was really whether, in a case where most compounds within a disclosed genus are determined to be enabled, do applicants bear the burden of providing evidence of efficacy for 100% of the compounds? Importantly, in the application at issue, there was no claim drawn to a method of treating a disease in humans (or animals), and no claim drawn to a pharmaceutical composition. Thus, the circumstances in *Bundy* are not commensurate with those surrounding the rejected claims of the instant application.

In the response filed 5/9/02, it is argued that the passage on page 20, line 4+ (specification) contributes to a showing of enablement because speculation is offered as to

what an appropriate dosage range might be, and because routes of administration are proposed. It is agreed that the skilled pharmacologist would be able to administer the claimed compounds. But the question is whether benefit would accrue to the patient afflicted with one of the diseases recited on page 3, line 31+. Merely because a compound can be administered does not mean that it will be effective in this regard, and speculation is not a replacement for factual scientific data.

In the response filed 5/9/02, reference is made to the following article:

> Brooks P. C. et al., "Requirement of vascular integrin alpha-v beta-3 for angiogenesis" (*Science* **264** (5158) 569-71, 1994).

The authors of this article demonstrated that an antibody to $\alpha_v\beta_3$ was indeed effective to inhibit angiogenesis in chick chorioallantoic membranes. However, the authors did not attempt to determine whether tumor volumes were reduced in a mature animal. Thus, based on this reference alone, it remains an open question as to whether a tumor-bearing rat (for example) would derive benefit from an antibody to $\alpha_v\beta_3$. It is also argued that Brooks provides a reference which shows that an antibody to an integrin was effective to treat restenosis in human patients. However, reference #24 is not a reference *per se*, but rather an assertion that J. N. Woody presented a paper at a conference held in San Diego sometime during 1993. Thus, neither the results obtained, nor the methods used, can be determined. Accordingly, it is not accurate to say that Brooks has established a correlation between $\alpha_v\beta_3$ antagonism and effective therapy of restenosis. In addition, in response to

the examiner's assertion of unpredictability based on Dechantsreiter (*J Med Chem*. **42**, 3033, 1999) and Haubner (*J Am Chem Soc* **118**, 7881, 1996), it is argued that these references are irrelevant because the compounds disclosed therein are not identical to any of those claimed. According to this line of reasoning, the disclosure of Brooks should be even more irrelevant, inasmuch as this reference is limited to experiments conducted on a monoclonal antibody, rather than a small organic molecule which is closely related to the tripeptide RGD. In addition it is argued that Haubner fails to disclose data on the propensity of peptides to inhibit the binding between the $\alpha_v\beta_3$ - integrin receptor, and a ligand. However, this is disclosed in table 2. In addition, at least one RGD-containing peptide failed to bind to each of two integrins. Thus, it remains the case that, where integrin/ligand binding is concerned, structure/activity relationships are unpredictable.

In the previous Office action, the examiner argued that *in vitro* antagonism of receptors is not necessarily indicative of *in vivo* efficacy. In response (response filed 5/9/02), it is argued that the examiner has provided no evidence that this is the case. However, the following five references support the examiner's assertion; these are discussed below: Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002); McFadyen (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61); Keith (*Molecular Pharmacology* **53** (3) 377-84, 1998); Xiao (*Biochemistry* **40**, 2860, 2001); and Lunec (*Melanoma Research* (1992 May) 2 (1) 5-12).

It is maintained that enablement is lacking for each of claims 5-8 and 21. As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Nature of the invention: The claims are drawn to compounds, pharmaceutical compositions, and therapeutic methods of use. The compounds are asserted to antagonize $\alpha_v$, $\beta_3$, and $\beta_5$ integrins. The method claims are drawn to treatment of patients who are afflicted with any of the following diseases/disorders: angiogenic disorders, "thrombosis", myocardial infarct, coronary heart disease, arteriosclerosis, tumors, osteoporosis, inflammation, or "infections". The nature of the "infections" is not specified but could potentially include infections due to bacteria, viruses, fungi or parasites.

State of the prior art:

The term "integrin" refers to a large family of heterodimeric adhesion molecules composed of *alpha* and *beta*-subunits; integrins play important roles in cell adhesion and migration, signal trnasduction and gene expression. Integrins are important for various biological functions including enbryonic development, cell growth, cell death and differentiation, and

immune responses. Because of the foregoing, integrin antagonism constitutes an area of research which might, at some point in the future, result in effective therapeutic methods. However, there is no evidence of record that antagonists of the $\alpha_{IIb}\beta_1$ or $\alpha_v\beta_3$ integrin can be used to treat ill patients who are afflicted with thrombolytic disorders, myocardial infarct, coronary heart disease, arteriosclerosis, cancer, osteoporosis, inflammatory disorders, or infections.

Relative skill of practitioners in the relevant arts: The level of skill required to practice the claimed invention is quite high. Research experise in both biochemistry and organic chemistry would be required. In addition, since the method claims are drawn to therapeutic methods, clinical expertise in each of the following would be required: oncology, immunology, allergies, infectious disease, cardiology and orthopedics.

Presence or absence of working examples: In a declaration filed 8/1/01 (part of paper No. 13), data is provided on three compounds. The compounds of examples 1-3 (page 22) were found to compete with biotinylated vitronectin for binding to placental tissue *in vitro*. No experiments were undertaken which provide direct evidence that the compounds can be used to treat any of the diseases which are listed in claims 7-8, and if so, what would have been the expected versus actual results of an *in vivo* test.

Amount of direction or guidance presented: The specification provides no guidance or direction about how to treat an ill patient who has been stricken with any of the following: thrombolytic disorders, myocardial infarct, coronary heart disease, arteriosclerosis, cancer, osteoporosis, inflammatory disorders, or infections. Even if it were true that one of these disorders could be successfully treated (and this has not been shown), it would not follow therefrom that the treatment conditions for the remaining disorders would be the same. One would expect very different treatment regimens for each of the cited disorders, and the specification does not provide direction for how to treat even one of them.

Breadth of the claims: It is not being argued that the breadth of the claims that are drawn to compounds *per se* is "undue"; however, the method claims (claims 7-8) do encompass a considerable range of pharmacological activities. Given the complexities of the various diseases recited, the breadth is quite considerable, and not adequately supported by the *in vitro* data provided such that an *a priori* expectation of success is present.

Predictability or unpredictability of the art:

As indicated above, success in the treatment of the disorders recited in claims 6-7 cannot be "predicted". To begin with, consider the following reference: Haubner (*J. Am. Chem. Soc.* **118**, 7881, 1996). This article discloses (table 2) two compounds which failed to

inhibit fibrinogen binding to the $\alpha_{IIb}\beta_1$ receptor, and vitronectin binding to the the $\alpha_v\beta_3$ receptor. The reference also discloses (p. 7882, col 2) that replacement of glycine with alanine in RGD results in a "drastic loss" of activity. As indicated above, it is stipulated that angiogenesis will be inhibited by the claimed compounds, and proliferation of tumor cells as well. But mere inhibition does not equate with a therapy. For a therapy to be "successful", the patient's condition must improve perceptively. Mere inhibition of angiogenesis and of tumor cell proliferation does not guarantee such success. No reference has been made of record which shows that an $\alpha_v\beta_3$ antagonist is effective to treat cancer in patients. Structure/activity relationships are unpredictable in the case of ligand/integrin interactions, and the degrec of $\alpha_v\beta_3$ antagonism by the claimed compounds may well be less than that of hypothetical compound. As indicated above, minor changes in structure can lead to complete loss of activity. While complete loss of activity is not being asserted, at least in the case of $\alpha_v\beta_3$ antagonism, some loss of activity may have occurred in making the transition from a hypothetical compound to the claimed compounds. In addition to the matter of unpredictability in the case of $\alpha_v\beta_3$ antagonism, there is also the matter of bioavailability/pharmacokinetics, and xenobiotic metabolism. These parameters will all change (in unpredictable ways) with structure of the compounds. Consider also the following:

- Nicosia (*American Journal of Pathology* **138** (4) 829-33, 1991) discloses that the peptide GRGDS is effective to inhibit angiogenesis, but that if the aspartic acid side

chain is extended by just one methylene group, loss of activity results. Thus, the conclusion is that structure/activity relationships are "unpredictable" where angiogenesis inhibition is concerned.

- Belo (*Inflammation* **25** (2) 91-6, 2001) discloses that thalidomide inhibited angiogenesis in mice, but failed to inhibit tumor growth in the same mouse strain.

- Mundhenke, "Tissue examination to monitor antiangiogenic therapy: a phase I clinical trial with endostatin" (*Clinical Cancer Research* **7** (11) 3366-74, 2001) disclosed the results of a phase I clinical trial with endostatin, which is an angiogenesis inhibitor. The result is that the endostatin was not particularly effective in treating cancer patients.

- Pignatelli (*Human Pathology* **23** (10) 1159-66, 1992) discloses that in breast carcinomas, expression of integrins is downregulated. This tends to suggest that if one makes "static" assumptions about the level of expression of integrins on tumor cells, an "unpredictable" outcome is likely.

Thus, one can conclude from the foregoing references that not only is it true that structure/activity relationships are "unpredictable" where angiogenesis inhibition is concerned, but in addition, even if angiogenesis can be achieved by a given compound "Z", success in the reduction of tumor volumes by the compound "Z" *in vivo* has been "unpredictable".

The following references disclose that stimulation or antagonism of a receptor *in vitro* does not necessarily correlate with *in vivo* efficacy:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]$NH_2$ (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4-D-Phe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

In accordance with the foregoing, it is clear that whether one is endeavoring to stimulate a

receptor *in vitro* or to antagonize a receptor *in vitro*, extrapolating to a therapeutic method leads to "unpredictable" results. While none of Torsello, McFadyen, Keith, Xiao, or Lunec discusses integrins specifically, the fact is that integrins are receptors, and if it is true that, in general, *in vitro* inhibition or stimulation of receptors leads to unpredictable results *in vivo*, one can expect the same for integrins.

- The method claims are drawn (in part) to a method of treating a disease which is, or results from "excessive platelet aggregration". One can look to the literature on thrombin antagonists for insight into the extent to which *in vitro* data correlates with efficacy in the treatment of thrombin-mediated disorders. As it happens, the outcome of therapy of thrombin-mediated disorders is often unpredictable, and does not necessarily correlate with in vitro activity. For example, Steinmetzer, T. et al, (*Expert Opinion on Investigational Drugs* **10** 845-64, 2001) discloses (e.g., abstract) that there are thrombin-mediated illnesses for which heparin, warfarin and aspirin are ineffective, even though these compounds exhibit antithrombic activity. The reference also discloses (page 857, col 2, last sentence) that there exists at least one compound which is an effective thrombin inhibitor in vitro, but is not effective in vivo. Moving onto another reference, Rutsch, W. et al (*European Heart Journal* **19** Suppl K, K11-K17, 1998) and Oldgren J. et al. (*European Heart Journal* **20** 1657-66, 1999) both convey that antithrombic compounds are not always effective in treating ill patients that are afflicted with thrombin-mediated disorders. Claim 7 is drawn to treatment of disorders resulting from excessive thrombosis; one can where such disorders are concerned, extrapolation from a result obtained *in vitro* can lead to an "unpredictable" result when attempted in an ill patient.

In view of the foregoing, it is clear that, at a minimum, treatment of cancer, angiogenic disorders, and pathological thrombosis cannot be predicted from *in vitro* integrin antagonism alone. Taken in conjunction with the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the

state of the prior art, the relative skill of those in that art, and the breadth of the claims, it follows that "undue experimentation" would be required of the skilled artisan to treat the various disorders recited in the claims.

*

Claims 1, 2, 4-8, 11-34 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 4 is indefinite as to the process steps. Specifically, the claim fails to recite an isolation step for the final product. If a chemist undertakes a chemical reaction (i.e., A + B → C), and if at the end of that reaction the product (i.e., "C") is present in a mixture which includes a solvent, and perhaps unspent reagents, the chemist is not in possession of product "C" *per se*. Instead, the chemist is in possession of a mixture that comprises "C". In the response filed 5/9/02, it is argued that an isolation step is not precluded. This rejection is directed at those embodiments for which isolation of the final is unrecited but is nevertheless needed in view of, e.g., claim 6 which is directed to a pharmaceutical composition.

- Claim 5 is rendered indefinite by its failure to recite a step for isolation of the final product. (See above).

- Claim 6 makes reference to "administration". What is the target of the administration? Is the target an animal, a plant, a petri dish, an apparatus, or something else?

- Claim 6 makes reference to "at least one excipient". On what basis does one determine the number of excipients present? For example, if one has a mixture of ten different compounds, does this correspond to one excipient, or ten?

- Claim 7 is indefinite with regard to which "diseases of the circulation" and which

"coronary heart diseases" are intended. For example, the following would be included. Which are intended?

atrial fibrillation, ventricular fibrillation, arteriosclerosis, artherosclerosis, angina, myocardial infarction, cardiomyopathy, endocarditis, hypertension, hypotension, myocardial ischemia, restenosis, thromboembolism, arrythmias, and heart failure.

- Claim 7 is indefinite as to the process steps and endpoint. Evidence has been provided which indicates that the $\alpha_v\beta_3$ integrin can be antagonized. According to the specification and subsequent arguments by applicants, antagonism of this integrin *necessarily* accompanies any successful treatment (of a disease). It is suggested that the claim be amended to recite that the time and conditions of the administration are indeed effective to antagonize the integrin in question. The same issue applies in the case of claim 8.

- Claim 7 is drawn (in part) to a method of treating tumors. A tumor, however, is not a disease *per se*, but rather a manifestation of a disease. Accordingly, the question is, what is the intended effect of the treatment?

- Claim 8 is indefinite with regard to the intended pathologies. One of the issues here is, how far "upstream" or "downstream" can one go in deciding whether the process is "supported or propagated" by angiogenesis.

- Claims 1 and 20 are indefinite with regard to the derivatives that might be intended. In the response filed 5/9/02, it is argued that the term "derivatives" is often used by chemists. However, there are many terms used in everday English, as well as terms used by chemists, that are indefinite. Consider, for example, the terms "hot", "cold", "near" and "far". These terms may be widely used, but their exact meaning is indefinite. It is maintained that the term "derivatives" renders the claims indefinite.

- Claim 32 is indefinite as to what a "reactive derivative" means. The claim is also rendered indefinite by the term "an agent suitable to achieve cyclization". In particular, if the "reactive derivative" were one in which the carboxyl group were derivatized to form an acid chloride, or an active ester, what reagent might be used

then to achieve cyclization?

- Each of claims 32-34 is rendered indefinite by its failure to recite a step for isolating the final product.

- In claim 33, the term "functional derivative" is used. The meaning of this is not clear. It is not clear, for example, which "derivatives" would not also be "functional".

*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is (703) 308-3213.

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

D.L. 7/29/02

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